Gene Therapy in Parkinson's Disease: A Review of Techniques and Clinical Outcomes

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Parkinson's Disease, a common mobility-related disorder among older people caused by the malfunction in the central nervous system, has been the focus of extensive research and treatment techniques over the years. Existing treatments for Parkinson's disease (PD) such as Levodopa (L-Dopa) address temporary symptoms but fail to aid long-term disease progression. These symptom-focused strategies are often accompanied by challenges including sudden unpredictable effects related to mobility, muscle degeneration, and most importantly a continued loss of dopaminergic neurons over time. With no current solution on how to halt disease progression, current research has turned towards disease-modifying therapies, focusing on neurotrophic factors, anti-aggregation therapies, and gene therapy. Among these, gene therapy has shown promise, utilizing various approaches to deliver neuroprotective genes or correct genetic mutations related to PD. This paper analyzes recent progress in gene therapy and evaluates how effective these methods are in clinical trials. It explores how these approaches could surpass the current treatment limits and help slow disease progression. By assessing the benefits and challenges, this paper shows how gene therapy could transform PD treatment and suggests ways to improve future clinical research and patient outcomes.

Keywords: Parkinson's disease, Gene Therapy, Dopamine, Neurological Disorder, Dopaminergic Neurons, Muscle Degeneration

Introduction

Parkinson's disease is a neurodegenerative disorder that primarily affects motor function due to the loss of dopaminergic (dopamine-producing) neurons in the substantia nigra, an important region of the brain that aids in regulating movement [1,2]. This deterioration significantly decreases dopamine levels and causes other damaging effects such as tremors, rigidity, bradykinesia (slowness of movement), and postural instability [3]. Moreover, PD patients can experience a range of non-motor symptoms, including cognitive decline, depression, and sleep disturbances. These symptoms significantly impact their quality of life [4]. Another key feature of PD is the abnormal aggregation of proteins, particularly alpha-synuclein into clumps (Lewy bodies), within the brain's neurons. These protein aggregates disrupt cellular function by interfering with mitochondrial activity, generating stress, and inhibiting protein degradation systems, ultimately leading to neuron death [5]. Currently, the most common treatment for PD only focuses on managing the symptoms rather than slowing down the progression of the disease. The administration of Levodopa (L-Dopa), a precursor to dopamine, is the most effective treatment for alleviating these symptoms. L-Dopa crosses the blood-brain barrier and replenishes the affected neurotransmitter [6]. While L-dopa effectively helps slow down motor symptoms, its long-term use is associated with side effects such as dyskinesia and other fluctuations [7]. Additional treatments, including deep brain stimulation and dopamine agonists provide symptomatic relief but do not halt disease progression or address the underlying cause of the disease [2].

Three main approaches have emerged as potential therapies: targeting neurotrophic factors, gene therapy, and anti-aggregation therapies. Neurotrophic factors are proteins that support the growth, survival, and differentiation of neurons. For PD, neurotrophic factors like glial cell line-derived neurotrophic factor (*GDNF*) and brain-derived neurotrophic factor (BDNF) have shown promise in protecting and promoting the survival of dopaminergic neurons, potentially slowing neuron degeneration [8,9]. Anti-aggregation therapies aim to prevent Lewy bodies, toxic aggregates composed of proteins such as alpha-synuclein. Therapies targeting alpha-synuclein aggregation aim to prevent or reduce this toxic build-up, thereby protecting neurons from damage [10]. Lastly, gene therapy involves the insertion of genetic material into cells to produce therapeutic proteins or to correct genetic mutations. Techniques such as adeno-associated virus (AAV)-mediated gene delivery, CRISPR-Cas9, and RNA interference (RNAi) are being studied for their potential to deliver neuroprotective genes or fix genetic abnormalities associated with PD. Given the limitations of current treatments, there is great potential for gene therapies to aid in slowing or stopping the progression of PD [11].

This paper will primarily focus on gene therapies, aiming to examine the clinical effects of different gene therapy techniques on PD progression and how these findings can improve the design and effectiveness of clinical trials for disease-modifying treatments. Through exploring these different methods, this review aims to provide an overview of the potential advantages and limitations. This paper also discusses the implications of these therapies for future research and clinical applications, overall showing the need to enhance our understanding of PD and patient outcomes.

Results

Promising Gene Therapy Techniques for PD Patients

Gene therapy techniques for PD provide a range of strategies that help in modifying gene expression or correcting genetic defects to slow down disease progression and alleviate symptoms. This section will provide a detailed examination of the leading techniques, including their mechanisms of action, clinical outcomes, and future goals. Highlighting the unique strengths and limitations of each approach offers insights into their impact on PD treatment and the obstacles that need to be overcome for successful results.

Adeno-Associated Virus Mediation

Adeno-associated viruses (AAVs) are small, non-enveloped viruses with a single-stranded DNA genome. They are approximately 20-25 nanometers in diameter and are known for their ability to infect a wide range of cell types without causing disease in humans [12]. AAVs enter target cells through endocytosis, where they bind to specific cell surface receptors and are internalized into the cell. Once inside, the viral capsid is broken down, allowing the viral DNA to be transported into the cell nucleus where it can be utilized for gene expression [13]. AAV-mediated gene delivery involves using AAVs as vectors to transfer therapeutic genes into target cells. AAV's are advantageous due to their ability to transduce a variety of cell types with minimal immune responses, including dividing and nondividing cells [14]. The process involves engineering the AAV vector to carry genes that encode therapeutic proteins, such as neurotrophic factors or enzymes, essential for dopamine synthesis directly into the brain. Once inside the brain, these genes are expressed, leading to the production of proteins that can protect dopaminergic neurons, counteract toxic processes in neural pathways, or enhance dopamine production.

One prominent example is the delivery of genes encoding neurotrophic factors such as the aromatic L-amino acid decarboxylase (AADC). The AAV2-AADC gene therapy aims to enhance dopamine synthesis by increasing the production of AADC, an enzyme that is essential in converting L-Dopa into dopamine. This technique occurs in the basal ganglia, a key area affected in PD, to restore dopamine levels and alleviate overall motor symptoms. AAV2-AADC gene therapy provides a potential solution to the diminishing efficacy of L-DOPA in PD by directly addressing the enzyme deficit responsible for dopamine synthesis. As PD progresses the degeneration of nigrostriatal neurons results in the loss of aromatic L-amino acid decarboxylase (AADC). This loss contributes to the diminishing effectiveness of L-DOPA, as the brain becomes less capable of synthesizing dopamine, even with adequate L-DOPA administration. The introduction of the AADC gene via the AAV vector has shown hopeful results in preclinical and early clinical trials. By using an AAV vector to deliver the AADC gene directly into the brain, the AADC therapy restores the enzymatic function necessary for the efficient conversion of L-DOPA into dopamine. This strategy provides several advantages over traditional L-DOPA therapy in the treatment of PD. Unlike systematic L-DOPA, which requires frequent dosing and loses efficacy over time as neuronal degeneration progresses, AAV2-AADC aims to provide long-term expression of the AADC enzyme in brain regions such as the basal ganglia. This approach ensures that L-DOPA is metabolized more efficiently into dopamine, reducing the need for escalating doses of L-DOPA and minimizing motor complications. Moreover, AAV vectors are minimally immunogenic, which reduces the risks of immune-mediated clearance, a key challenge in gene therapy. This is important given the need for sustained enzyme expression time for the therapy to be effective. Furthermore, AAV vectors' ability to transduce or transfer genetic material from one bacterium to another, from both dividing and non-dividing cells, aids the therapy to reach neurons in regions like the putamen, where the neurodegenerative process is most severe. Unlike L-DOPA, which only provides temporary symptomatic relief without addressing neuronal damage, AAV2-AADC therapy offers potential for disease modification by offering a more durable, long-term solution by addressing the root cause of the dopamine deficiency and providing localized production of dopamine from within the brain. AAV2-AADC enables more stable and sustained dopamine production, reducing the need for high medication, making it a strong candidate for advanced PD patients despite halts about L-DOPA administration.

Clinical trials have demonstrated that AAV2-AADC therapy can significantly improve motor symptoms and reduce reliance on dopaminergic medications [15]. Christine et al. (2009) reported that patients experienced reduced motor symptoms and decreased reliance on dopaminergic medications. However, the sustained efficiency of the AAV2-AADC gene therapy is a major concern as the therapy's benefits may diminish over time. The continuation of gene expression and vector stability in the brain is crucial, and there is a risk that the AAV vector may lose its effectiveness or that the AADC enzyme may degrade. Additionally, the immune system's response to the AAV vector could impact long-term outcomes, potentially leading to reduced efficacy or adverse effects such as inflammation. Parkinson's

Disease itself is progressive, which means that while the therapy may alleviate symptoms initially, it may not halt disease progression. Therefore, the long-term impact on motor symptoms and overall disease course needs further investigation. Continued research and long-term clinical trials are essential in ensuring the therapy is helpful in managing the outcomes of PD[16].

Another key example is the AAV2-*GDNF* gene therapy which introduces the *GDNF* gene to support the survival and function of dopaminergic neurons. This gene is known to promote neuronal growth and protect against neurotoxicity, mitigating the degeneration of dopaminergic neurons. This gene works by binding to its receptor, GFR1, which then interacts with the RET (Rearranged during Transfection) receptor, a tyrosine kinase. This interaction activates several key signaling pathways that help protect and sustain neurons. One is the PI3K/Akt pathway, which prevents cell death by blocking pro-apoptotic proteins like BAD and caspase-9. Another important pathway, MAPK/ERK, enhances neuronal growth, synaptic plasticity, and dopamine release. Additionally, the mTOR pathway plays a role in promoting protein synthesis and neuronal regeneration. Together, these mechanisms help shield neurons from degeneration and support their long-term health.

Preclinical and early clinical trials, such as those by Marks et al. (2010), have shown that AAV2-*GDNF* can promote neuronal survival and improve motor function. Preclinical studies utilizing rodent and non-human primate models have demonstrated that AAV2-*GDNF* significantly enhances dopamine neuron survival, increases dopamine production, and improves behavioral deficits. In non-human primates, PET imaging studies have confirmed increased dopamine transporter (DAT) expression in the striatum following AAV2-*GDNF* administration, indicating enhanced dopaminergic activity. Despite these promising results, there have been mixed outcomes in clinical trials, and some studies have faced challenges with patient selection and therapy administration. For instance, some clinical trials have shown that although *GDNF* therapy increases dopamine transporter density, it does not always translate to significant motor improvement, possibly due to inadequate distribution of the therapy within the putamen. Variability in patient responses and difficulties in delivering the gene therapy precisely to the affected brain regions have contributed to inconsistent results. Addressing these challenges is possible by refining criteria for selecting patients who are most likely to benefit from AAV2-*GDNF* gene therapy, enhancing delivery methods to ensure the gene therapy reaches the intended areas of the brain effectively, and monitoring for long-term safety and efficacy[17].

Future research in the study of this technique aims to develop next-generation AAV vectors with enhanced targeting specificity and reduced immunogenicity. Along with that researchers are hoping to investigate combination therapies that integrate AAV-mediated gene delivery with other neuroprotective or disease-modifying treatments such as dopamine agonists, deep brain stimulation, and *LRRK2* inhibitors, to address the complexity of PD[18,19].

Researchers are also exploring advanced delivery methods to improve the effectiveness of AAV2-*GDNF* therapy. Controlled-release systems and optimized viral vectors, such as AAV9, are being developed to ensure better distribution of *GDNF* within the striatum and prolong its therapeutic effects. To assess the impact of this treatment over time, imaging techniques like functional MRI and PET scans are being used. These tools allow scientists to monitor how well the therapy is working in real time, helping to fine-tune dosing strategies and track disease progression more.

CRISPR-Cas9 Genome Engineering

CRISPR-Cas9 gene editing is another gene therapy approach that uses a guide RNA (gRNA) to direct the Cas9 endonuclease to specific DNA sequences, producing double-strand breaks. These breaks are repaired through cellular mechanisms, which can be harnessed to correct genetic mutations or disrupt disease-associated genes[20]. In PD, CRISPR-Cas9 can target genes such as *LRRK2*, hence mutations in this gene are linked to familial PD. CRISPR-Cas9 can be used to correct these mutations, potentially halting the disease's progression by repairing or disrupting the mutated *LRRK2* gene. Preclinical studies have successfully used CRISPR-Cas9 to correct *LRRK2* mutations in animal models, leading to reduced neurodegeneration and improved motor function[21]. Clinical trials are in the early stages, and challenges include ensuring precise editing and minimizing off-target effects.

Off-target effects occur when CRISPR-Cas9 unintentionally edits genes other than the intended target, which can lead to harmful genetic alterations, including frameshift mutations, chromosomal rearrangements, or activation of oncogenes that may increase cancer risk. Strategies to minimize these risks include optimizing guide RNA design using computational prediction models to enhance target specificity and using high-fidelity Cas9 variants, such as SpCas9-HF1 and eSpCas9, which have been engineered to reduce off-target activity while maintaining efficient genome editing. Additionally, base editing and prime editing techniques have emerged as promising alternatives to traditional CRISPR-Cas9, as they enable precise single-nucleotide modifications without inducing double-strand breaks. This reduces the likelihood of unintended mutations[22].

Additionally, as mentioned earlier, alpha-synuclein aggregation forms Lewy bodies. CRISPR-CAs9 can target the *SNCA* gene to reduce the production of alpha-synuclein to prevent the formation of toxic aggregates. CRISPR-Cas9 has been used in preclinical models to reduce alpha-synuclein levels and mitigate associated neurotoxicity, leading to improved neuron survival and motor function. (Koch et al., 2021). This technology shows significant potential, as reducing alpha-synuclein production directly addresses the underlying pathology of PD by preventing neurodegeneration and preserving dopaminergic neurons.

However, it requires further validation in human trials to address safety concerns and efficacy, to ensure that the therapy effectively targets the *SNCA* gene without causing unintended genetic modifications, thereby maximizing its therapeutic benefits while minimizing risks. Specifically, future research needs to enhance gene editing accuracy by reducing off-target modifications and developing more effective delivery systems for targeting neurons in the brain[23].

Beyond off-target effects, another major challenge with CRISPR-Cas9 is the immune response it can trigger. Since the Cas9 protein comes from bacteria like Streptococcus pyogenes, the human immune system may recognize it as a foreign invader, leading to inflammation or reduced gene-editing efficiency. Some studies have even found that people already have antibodies and T-cell responses against Cas9, which could make treatment less effective. To work around this, researchers are exploring ways to modify the Cas9 protein to make it less detectable by the immune system. One approach is using Cas9 enzymes from less common bacterial strains, while another involves engineering humanized versions of Cas9 that are less likely to trigger an immune response. Scientists are also looking into immunosuppressive treatments and nanoparticle-based delivery systems to help shield CRISPR components from immune attack, increasing the chances of a successful therapy.

Moving forward, research should focus on refining gene-editing techniques to improve precision and reduce risks, while also enhancing delivery methods to ensure CRISPR reaches target neurons without being neutralized by the immune system. Tackling these challenges is essential for transitioning CRISPR-Cas9 from the lab to a viable treatment for PD.

RNA Interference

Another technique, RNA interference (RNAi), uses small RNA molecules to regulate gene expression after transcription. One example of RNAi is Small interfering RNAs (siRNAs), which are designed to specifically target and degrade mRNA transcripts of disease-related genes. By using siRNAs to target a gene such as *SNCA* mRNA, RNAi aims to reduce the production of alpha-synuclein, thereby decreasing its aggregation and associated neurotoxicity[24]. Preclinical studies have demonstrated that RNAi can effectively reduce alpha-synuclein levels and improve neuronal health in animal models[25]. Clinical research is ongoing, with several significant challenges.

One major issue is the efficient delivery of RNAi molecules to the central nervous system. The blood-brain barrier (BBB) poses a significant obstacle, making it difficult for RNAi agents to penetrate and reach target neurons[26]. Additionally, ensuring specific and sustained gene silencing is challenging. RNAi molecules must accurately target disease-related mRNA while avoiding unintended effects on other genes[27]. RNA instability and degradation further complicate the process, as RNA molecules are susceptible to rapid breakdown by cellular enzymes, requiring strategies to improve their stability and protect them during delivery[28]. Future developments for RNAi include improving delivery systems, such as using lipid nanoparticles or advanced viral vectors, to enhance brain penetration and therapeutic efficacy, and finding ways to increase the stability and specificity of RNAi molecules to reduce off-target effects[29].

Antisense Oligonucleotides-based Modulation

Antisense Oligonucleotides (ASOs) are short, synthetic nucleic acid sequences designed to bind to specific mRNA molecules, to modulate gene expression. By annealing to their target mRNA, ASOs can inhibit translation or promote degradation of the mRNA, thereby reducing the production of the corresponding protein[30]. This approach allows for the targeted suppression of genes associated with disease. For PD, ASOs can be designed to target mRNA transcripts of genes involved in neurodegeneration, such as alpha-synuclein, with the goal of decreasing the production of toxic proteins and mitigating disease progression. Preclinical studies have shown that ASOs can effectively reduce the levels of target proteins and improve disease-related outcomes in animal models. However, challenges include ensuring effective delivery to the central nervous system, avoiding off-target effects, and achieving sustained expression of the ASO to maintain therapeutic benefits[31]. Ongoing research aims to refine delivery methods and enhance the stability and specificity of ASOs to optimize their therapeutic potential[32].

The overarching goal for all techniques is to develop therapies that not only alleviate symptoms but also modify the disease course. Advancements in delivery technologies, precision targeting, and safety profiling are essential. Combining these techniques with other therapeutic strategies may offer a comprehensive approach to treating Parkinson's disease.'

In summary, each gene therapy technique presents unique opportunities and challenges. AAV-mediated delivery is currently the most established, while CRISPR-Cas9 holds significant potential for precise gene editing. RNAi and ASOs provide alternative approaches with ongoing research needed to optimize their clinical application[33]. Continued advancements in technology and integration of these techniques will be crucial for achieving effective and long-lasting treatments for Parkinson's disease.

Factors Influencing Gene Therapy Outcomes

The success of gene therapies in treating PD depends on various factors that can significantly influence therapeutic outcomes. These factors can include genetic variability, gender, delivery methods, and environmental factors. Understanding how these elements impact clinical responses is essential to developing more effective and personalized treatments for PD patients. This section will explore how these factors shape therapeutic outcomes and discuss advancements in design, delivery technologies, and medical approaches to enhance treatment efficacy and safety.

Table 1 Overview of Gene Therapy Techniques for Parkinson's Disease

Technique	Mechanism	Advantages	Challenges
CRISPR-Cas9	Precise gene editing at the DNA level	High precision, targeted modifications	Off-target effects, delivery difficulties
AAV-Mediated Delivery	Viral vectors for gene delivery	Advanced delivery system, effective in various tissues	Immune responses, long-term expression issues
RNA Interference (RNAi)	Targeting RNA to modulate protein levels	Ability to silence specific genes	Stability, brain penetration, immune response
Antisense Oligonucleotides (ASOs)	Targeting RNA to alter gene expression	Potential for high specificity	Early-phase trials, stability, delivery challenges

Table 2 Comparative Analysis of Gene Therapy Techniques

	Delivery Efficiency	Clinical Readiness	Specificity and Safety
CRISPR-Cas9	Experimental, evolving methods	Experimental, ongoing research	High precision, off-target effects
AAV-Mediated Delivery	Clinically advanced, delivery response issues	Most advanced, trials showing efficacy	Effective, potential immune response
RNA Interference (RNAi)	Requires improved mechanisms	Experimental, needs validation	Specificity issues, immune response potential
Antisense Oligonucleotides (ASOs)	Needs better delivery solutions	Promising but early-phase	Promising specificity, requires development

Genetic Variability

Genetic variability significantly influences therapy outcomes and treatment designs in PD. Both genetics and environmental components are prevalent in PD, a multifactorial disease. Specific genetic variants such as those in the *SNCA*, PARK2, and *LRRK2* genes significantly affect how patients respond to gene therapy[34]. For example, patients with certain distinct genetic profiles such as *LRRK2* mutations may benefit more from therapies targeting neuroprotective genes like *GDNF* or brain-derived neurotrophic factors (BDNF), compared to those with the *SNCA* variants, who might require different therapeutic approaches[35].

This means gene therapy must be personalized based on a patient's genetic makeup. For instance, the expression level of therapeutic transgenes, immune response to vectors, and distribution of the viral vector in the brain can all vary depending on the genetic profile. A patient with PARK2-related PD may respond poorly to therapies designed for *SNCA* overexpression, due to differences in underlying molecular mechanisms such as mitochondrial function versus alpha-synuclein aggregation.

These differences can also influence how patients metabolize or respond to the inserted genetic material[36]. To account for these differences in treatment design, genetic screening and stratification prior to therapy initiation is essential. Clinical trials should incorporate genetic profiling to group participants by key variants such as *LRRK2* or *SNCA*, allowing for the testing of variant-specific therapies. Furthermore, vector dosage, delivery method, and therapeutic targets can be adjusted to optimize efficacy for specific genotypes. These considerations emphasize the need for genetic matching or adjustments in study designs[37].

Sex differences also influence the outcomes of gene therapy for PD. Men have a 1.5 to 2 times higher chance of developing PD than women and often experience more severe motor symptoms. This extends into gene therapy responses, which may require gender-specific considerations in future treatment designs. Hormonal changes between men and women may also affect gene expression and therapeutic impact. For example, estrogen has been shown to modulate the expression of neuroprotective genes and influence neuroinflammatory responses, which could impact how effectively gene therapies function in women compared to men[38]. Additionally, differences in sex chromosome-linked gene expression may affect vector uptake and distribution in neural tissues, resulting in differential efficacy. For instance, females may experience enhanced neuroprotection due to estrogen's interaction with genes like *GDNF*, suggesting that gene therapies targeting neurotrophic pathways could yield better outcomes in women. Using approaches that optimize outcomes for both genders and taking these hormonal differences into account are crucial considerations for improving the efficiency of gene therapy treatments[39]. Therefore, designing gender-responsive gene therapies—such as tailoring vector types, delivery sites, and timing around hormonal cycles or using sex-specific promoters—could enhance therapeutic effectiveness and minimize adverse effects. Future studies should include sex as a biological variable in both preclinical and clini-

cal phases to guide precision treatment strategies.

Environment

Environmental factors play a significant role in influencing the outcomes of gene therapy for PD. Exposure to environmental toxins, such as pesticides and heavy metals, has been linked to an increased risk of developing PD. These environmental influences can affect the disease's progression and potentially impact gene therapy's effectiveness. For instance, ongoing exposure to neurotoxicants may counteract the benefits of gene therapy by continuously damaging neurons and interfering with therapeutic processes[40].

Delivery Techniques

The method of delivery is critical in determining the success of gene therapy. Various delivery techniques have their advantages and challenges. The intracerebral injection delivers the therapeutic genes directly into the brain, ensuring targeted delivery but being highly invasive and carrying risks such as infection and inflammation. Intravenous administration is less invasive but faces challenges with the blood-brain barrier, limiting the number of therapeutic genes reaching the target neurons[41]. Intranasal delivery offers an alternative that allows therapeutic regents to be absorbed through the nasal mucosa, however, this method faces challenges related to dosage amounts. Recent advancements in delivery technologies, such as nanoparticles and viral vectors like AAV, are showing promise in improving the efficiency and specificity of gene delivery to the brain[42].

Advancements in the design of gene therapy techniques are critical for enhancing treatment efficacy and safety. This includes the development of more sophisticated viral vectors that can deliver genes more precisely and with fewer side effects[43]. Improvements in the regulation of gene expression, such as the use of promoters that can turn the therapeutic gene on or off in response to specific signals, can help mitigate potential risks associated with gene therapy. Additionally, combining gene therapies with other clinical approaches, such as neuroprotective drugs or anti-inflammatory agents, can provide a well-rounded approach to treating PD. Such combination strategies can address multiple aspects of the disease, potentially leading to better patient outcomes. Analyzing the latest research will provide insights into their integration into treatment protocols[44].

Information Technology

Gene therapy for PD is a rapidly evolving field, with recent advances aiming to address the underlying genetic and molecular genetic mechanisms of neurodegeneration. However, patient selection, therapy monitoring, and treatment outcomes prediction remain major challenges. Artificial Intelligence (AI), machine learning (ML), and big data analytics are increasingly being employed to optimize these aspects of gene therapy to increase the precision and efficacy of treatment strategies.

AI has shown promise in predicting individual responses to gene therapy, leveraging multi-modal patient data to tailor dosage, vector selection, and administration timing. Bayesian inference models and reinforcement learning frameworks have been employed to optimize AAV vector delivery, reducing the risk of immune responses and off-target effects. Moreover, graph neural networks (GNNs) are being utilized to map genetic and molecular interaction networks, facilitating in silico predictions of how specific genetic variants modulate gene therapy efficacy[45].

Effective gene therapy relies on the ability to identify optimal patient subgroups who will gain the most benefit from treatment. Traditional clinical and genetic screening approaches are limited by their reliance on single biomarker associations and small, heterogeneous patient cohorts. AI, particularly deep learning applied to multi-omic datasets, has demonstrated superior predictive capabilities in stratifying PD subtypes based on polygenic risk scores (PRS), transcriptomic variations, and neuroimaging biomarkers. Furthermore, unsupervised clustering models applied to large scale genomic data, such as UK Biobank and PPMI, have revealed previously unrecognized genetic subtypes of PD that correlate with differential responses to neuroprotective therapies, However challenges persist in terms of cohort diversity, feature selection bias, and generalizability of AI models across populations.While dataset consistency is an important prerequisite to these techniques, data heterogeneity is a major challenge, as genomic and clinical datasets often come from different sources with varying formats, quality, and labeling standards. This lack of uniformity complicates the training of AI models and limits their ability to generalize across different patient populations[46].

Gene therapy for PD necessitates longitudinal monitoring to assess therapeutic efficacy and detect potential adverse events. Traditional clinical endpoints such as the Unified Parkinson's Disease rating Scale (UPDRS) are inherently subjective and sparse, limiting their utility in high resolution therapy tracking. AI-driven sensor fusion models, integrating wearable accelomtrey, electrophysiological recording, and patient-reported outcomes provide a more granular, continuous assessment of disease progression. In parallel, convolutional neural networks (CNNs) applied to neuroimaging modalities, including diffusion tensor imaging (DTI) and functional MRI (fMRI), have enhanced the detection of neuroanatomical changes following gene therapy administration. However these AI models suffer from high inter-subject variability, batch effects in image acquisition, and the lack of standardized validation frameworks, highlighting the needs for federated learning approaches to harmonize multicenter data[47].

Ethical concerns surrounding genomic data privacy also present a major barrier. AI-driven gene therapy relies on vast amounts of patient-specific genetic information, raising questions about data security, consent, and equitable access. Regulatory frameworks must evolve to ensure patient rights are protected while still allowing researchers to develop effective AI models. Additionally, interpretability of inference engines

remains a challenge. Many AI models, particularly deep learning systems, function as "black boxes," making it difficult for clinicians to understand how decisions are being made. Without greater transparency, regulatory approval and clinical adoption will be hindered.

Impact and Outcomes of Gene Therapy Trials on Parkinson's Disease

Gene therapy trials for PD have shown significant potential in managing symptoms and potentially altering the track of disease progression. These therapies focus on targeting the genetic and biochemical pathways underlying PD, overall aiming for long-term benefits and improved quality of life for patients. This section reviews the outcomes of several notable gene therapy trials, highlighting their long-term implication, efficiency, and safety.

1. Provasin®, developed by Oxford BioMedica, is a gene therapy that delivers three genes encoding for enzymes required for dopamine synthesis using a lentiviral vector[48]. Clinical trials of Provasin® have shown moderate improvements in motor function, as indicated by the Unified Parkinson's Disease Rating Scale (UPDRS) scores[49]. In a phase I/I trial, patients exhibited an average improvement of 27% in UPDRS scores post-treatment. Some patients even maintain improvements for up to three years. The therapy was well-tolerated with only mild to moderate side effects such as headaches, nausea, and dizziness, suggesting that Provasin® can provide significant motor benefits in PD patients. A Phase 2 trial (NCT03562494) assessed its safety and efficacy in patients with moderate to advanced PD, with results showing improved motor function and reduced medication needs.

2. AXO-Lenti-PD, another lentiviral vector-based gene therapy, has also shown promising results. This therapy delivers three genes that encode enzymes involved in dopamine synthesis, aiming to restore dopamine levels in the brain[13]. Early-stage trials reported significant reductions in UPDRS scores, with improvements maintained over several months[50]. In a phase I/II study, patients experienced a mean improvement of 29% in UPDRS scores at six months post-treatment, with some patients showing sustained benefits for up to 12 months. The safety profile of AXO-Lenti-PD was favorable, with patients experiencing only transient headaches and fever, suggesting a well-tolerated therapy with potential long-term benefits. A Phase 2 trial (NCT03720418) is evaluating its long-term safety and clinical benefits, following promising early-phase data.

3. Ceregene's Glutamic Acid Decarboxylase (GAD) gene therapy aims to increase the production of gamma-aminobutyric acid (GABA) in the brain to improve motor control. Phase II trials of GAD gene therapy demonstrated modest improvements in motor function, with a 23% improvement in UPDRS scores at six months post-treatment[51]. The therapy was deemed safe, with only minor side effects such as headaches and local site reactions reported. These results indicate that GAD gene therapy can offer motor benefits and is generally well-tolerated. A previous Phase 2 study (NCT00643890) showed motor improvement, though further development was limited.

4. Voyager Therapeutics' AAV2-hAADC therapy involves the delivery of the aromatic L-amino acid decarboxylase (AADC) gene using an adeno-associated viral (AAV) vector. This therapy aims to enhance the conversion of levodopa to dopamine, thereby improving motor function and reducing "off" periods, also known as the time frame in which patients, are off medications and symptoms appear to return or worsen. A Phase 2 trial (NCT03562494) assessed its safety and efficacy in patients with moderate to advanced PD. Clinical trials have shown marked improvements in motor function, with UPDRS scores improving by an average of 25% at six months post-treatment[52]. Additionally, patients experienced a significant reduction in "off" periods, enhancing their quality of life. The therapy was generally safe, with no serious adverse events and only mild side effects such as headaches and dizziness[53].

5. Prevail Therapeutics' *LRRK2* gene silencing therapy targets a gene mutation associated with familial PD, aiming to slow disease progression and stabilize motor symptoms. Preclinical studies have shown that *LRRK2* silencing can reduce alpha-synuclein aggregation and neuroinflammation, key pathological features of PD[54]. Early-phase clinical trials have indicated potential benefits in slowing disease progression and improving motor function, with patients showing a mean improvement of 20% in UPDRS scores at six months post-treatment[55]. The safety profile was good, with mild side effects such as transient fatigue and injection site reactions reported. The PROPEL Phase 1/2 trial (NCT04127578) is ongoing to evaluate safety, biomarker response, and motor function improvement.

The table below provides a summary of methodological frameworks, patient inclusion and exclusion criteria, and study designs, including sample size, study duration, and control groups, for all discussed gene therapy clinical trials in Parkinson's disease.

Analysis of results of Gene Therapy Trials on Parkinson's Disease

Analyzing the outcomes of these trials highlights that while gene therapy presents promising results, it often falls short in

Table 3 Overview of Methodological Frameworks, Patient Criteria, and Study Designs for Gene Therapy Trials in Parkinson's Disease

Study	Methodological Framework	Patient Exclusion, Inclusion Criteria	Sample Size	Study Duration	Control Group
Provasin®, developed by Oxford BioMedica	Open-label, dose-escalation, Phase I/II trial	Inclusion: - Age between 48 and 65 years - Disease duration of at least 5 years - Hoehn and Yahr stage 3 or 4 in the off state - UPDRS part III (off) scores between 20 and 60 - Motor complications associated with L-Dopa therapy - Stable medication regimen for at least 4 weeks prior to surgery - $\geq$50% improvement in UPDRS part III score between off and on states in response to an acute L-Dopa challenge Exclusion: Patients were followed up for a minimum of 6 months post-treatment, with long-term follow-up extending to 4 years for some participants.	15	Patients followed up 6 months post-treatment; extending to about 4 years	No control group
AXO-Lenti-PD	Phase 1/2 open-label, dose-escalation study	Inclusion: - Diagnosed with idiopathic PD. - Levodopa-responsive with at least 5 years of treatment history. - Experiencing motor fluctuations and dyskinesias inadequately controlled by current therapy. Exclusion: - Presence of significant cognitive impairment or dementia. - History of neurosurgical interventions for PD. - Other severe neurological disorders or medical conditions that could interfere with study participation.	Cohort 1: 4 subjects Cohort 2: 2 subjects	6 months	No control group
GAD	Phase 2, double-blind, randomized, placebo-controlled trial	Diagnosed with idiopathic PD with significant motor fluctuations. - Levodopa-responsive PD with at least a 5-year history. - Hoehn and Yahr Stage 3 or less while on medication. - Age 30-75 years. Exclusion: - Dementia or significant cognitive impairment (Mini-Mental State Examination (MMSE) ¡24). - Prior neurosurgical intervention for PD (e.g., Deep Brain Stimulation). - Severe comorbidities that might interfere with participation. - Use of investigational treatments within 6 months before enrollment.	45	6 months	Sham-surgery group
Voyager Therapeutics' AAV2-hAADC	Phase 1b, open-label, dose-escalation clinical trial	Inclusion: - Idiopathic PD with severe motor fluctuations and suboptimal response to levodopa. - Disease duration of at least 5 years. - Hoehn and Yahr Stage 3 or 4 in the off-medication state. - Age 40-70 years. Exclusion: - Cognitive impairment or dementia (Montreal Cognitive Assessment (MoCA) ¡26). - Prior deep brain stimulation (DBS) surgery or significant brain abnormalities. - Severe medical comorbidities	15	12 months	Patients compared to baseline and PET imaging results before treatment
Prevail Therapeutics' *LRRK2* gene silencing	Prospective, open-label, ascending dose study.	Diagnosis of PD with at least one GBA1 mutation.	20	Started January 3, 2020; estimated to complete in June 2029.	No control group

demonstrating long-term safety and efficacy in slowing disease progression and managing symptoms in PD. Most therapies have shown favorable outcomes in managing motor symptoms, improving UPDRS scores, and reducing "off" periods, thereby enhancing the quality of life for patients. For instance, both Prosavin® and AXO-Lenti-PD therapies demonstrated sustained motor improvements, suggesting long-term benefits. Similarly, Voyager Therapeutics' AAV2-hAADC therapy not only improved motor function but also reduced "off" periods, indicating a substantial impact on daily living[56].

Some studies have also reported secondary benefits in non-motor symptoms such as mood and cognitive function, though these findings are less consistent. For example, some patients in the Prosavin® trial reported improvement in mood and cognitive function, although these effects were not universally observed. Further research is needed to fully understand the impact of gene therapy on non-motor symptoms[57].

Current clinical landscapes are shaped predominantly by early-phase trials, which constrains the ability to draw firm conclusions about its long-term viability. The small scale and design of these studies do more than just limit statistical power, they create an environment in which observed improvements may reflect study design artifacts rather than true therapeutic effects. Without proper controls, it becomes difficult to distinguish between actual biological responses and placebo-driven outcomes, particularly in a disease like PD where symptom fluctuation is common. Moreover, the short duration of most trials does not allow for an adequate understanding of whether the therapeutic gene remains active over time or whether initial improvements plateau or decline. For example, while the Prosavin® trial generated early enthusiasm, its lack of a control arm and long-term follow-up meant that questions about the durability of gene expression and the emergence of late adverse events could not be addressed[58]. Additionally, the open-label nature of these trials increases susceptibility to placebo effects and observer bias, further complicating the evaluation of true treatment effects. Crucially, early-phase trials typically do not account for long-term safety concerns, including delayed immune responses, vector-related toxicity, off-target genetic effects, or the persistence of therapeutic gene expression. Studies such as the AADC gene therapy trial have demonstrated preliminary safety and efficacy signals; however, without rigorous control conditions and extended monitoring, these findings remain preliminary and cannot yet inform clinical practice[59]. Therefore, there remains a need for well-powered, randomized, placebo-controlled, and long-term studies to validate early findings and fully assess the utility and safety profile of gene therapy in PD.

While early-phase gene therapy trials for Parkinson's disease have often emphasized safety and potential motor improvements, several have failed to demonstrate durable or clinically significant efficacy. Notably, the Phase II trial of AAV2-GAD gene therapy, which targeted the subthalamic nucleus to enhance GABA production, did not show statistically significant differences compared to the sham group, despite early-phase enthusiasm. This outcome raised important questions about not only vector delivery efficiency but also target selection and the biological relevance of modulating specific pathways in advanced PD[60]. Similarly, ProSavin reported only modest motor improvements without placebo controls, making it difficult to assess clinical significance. Moreover, the lack of sustained benefit in some patients suggests that transgene expression may decline over time, potentially due to vector silencing or progressive neurodegeneration in untreated areas. These outcomes contrast with more recent trials employing AADC gene therapy, which have shown more consistent symptom improvement, though still in open-label designs with small cohorts. The varying efficacy between approaches may be influenced by differences in transgene targets, vector types, and delivery routes highlighting the importance of comparative studies with uniform endpoints. To advance the field, future trials must incorporate rigorous controls and head-to-head comparisons between different gene therapy strategies to clarify which mechanisms offer the most meaningful and sustainable outcomes.

Long-term follow-up data for gene therapy in PD are still limited, which makes it difficult to fully assess the durability of treatment effects. For example, a randomized, double-blind, sham-controlled trial using AAV-GAD gene delivery to the subthalamic nucleus in 45 PD patients showed safety and motor improvements at 12 months, but longer-term outcomes remain unknown. This lack of extended data raises concerns about whether initial benefits can be sustained and whether new risks may emerge over time. To address these challenges, several strategies have been proposed. Repeat dosing could help maintain therapeutic gene expression, although immune responses to viral vectors may complicate this approach. Combination therapies, such as using neuroprotective agents or dopamine agonists alongside gene therapy, may also boost overall effectiveness. Additionally, adjunctive treatments like anti-inflammatory drugs could reduce immune reactions and help prolong therapeutic effects. Including these strategies in future trial designs could improve the long-term success and practical use of gene therapy in clinical settings.

Several trials have encountered setbacks due to safety concerns, inconsistent efficacy, and patient variability. For example, the Phase 2 trial of AAV2-GAD (Ceregene), despite initial motor symptom improvement, failed to show long-term benefits over the sham group. Voyager Therapeutics' AAV2-hAADC trial showed early promise, but some patients experienced off-target effects and inflammation. Prevail Therapeutics' *LRRK2* gene silencing therapy raised concerns about unintended cellular disruptions. These challenges highlight the need for refined trial designs, improved vector delivery, better patient stratification, and robust biomarkers to ensure long-term success[61].

Ultimately, mixed or inconclusive results from various gene

therapy trials underscore the importance of optimizing delivery methods, refining patient selection criteria, and improving strategies for maintaining long-term efficacy.

Discussion

Gene therapy, through its innovative strategies and targeted interventions, holds significant promise for altering the course of PD, offering new avenues for symptom management and potentially modifying disease progression. This review has examined the potential of gene therapy as a transformative approach to managing Parkinson's Disease, highlighting both its current capabilities and prospects. As we look to the future, several research goals are pivotal in advancing gene therapy techniques for Parkinson's Disease.

First, improving delivery methods remains a top priority. Developing more efficient and targeted delivery systems capable of crossing the BBB, such as advanced viral vectors or nanoparticle-based approaches, will be crucial in ensuring that therapeutic genes reach their intended targets in the central nervous system with minimal off-target effects.

Second, personalization of therapies based on genetic profiles and individual patient characteristics is essential. Tailoring gene therapies to account for genetic variability and gender differences can enhance therapeutic outcomes and minimize adverse effects, leading to more effective and individualized treatments.

Third, addressing long-term efficacy and safety concerns is vital. Patient heterogeneity, including genetic variations and differences in disease progression can impact treatment efficacy. Vector delivery issues, such as inconsistent transgene expression and limited brain penetration, pose additional hurdles. Immune responses to viral vectors may reduce effectiveness and lead to adverse effects. Sustained gene expression remains uncertain, raising concerns about long-term benefits and safety. These challenges highlight the need for further refinement in gene therapy approaches, ensuring better patient selection, improved vector design, and long-term monitoring for safety and efficacy61. Ongoing research should focus on understanding the long-term impacts of gene therapies, including their durability and potential for immune responses or other adverse effects. This includes refining existing techniques and exploring new approaches to extend the benefits of gene therapies over time.

Fourth, the use of Artificial Intelligence can boost the overall understanding of patterns of progressions based on patient profiles and thus lead to an effective treatment selection. This requires collecting data such as UPDRS and other test scores, images, and profile information for a large set of patients over a long period. The ongoing work from Parkinson's Progression Markers Initiative (PPMI) in collaboration with the Michael J Fox Foundation can provide the foundational data sets needed for AI model training.

Finally, integrating gene therapies with other treatment modalities could offer comprehensive solutions for managing Parkinson's Disease. Combining gene therapies with pharmacological treatments, physical therapy, or other supportive measures may provide benefits and improve overall patient outcomes.

In conclusion, gene therapy stands at the forefront of innovative approaches to Parkinson's Disease management, with the potential to significantly impact disease progression and quality of life. Continued research and development in this field are essential for refining these techniques, overcoming current challenges, and realizing the full potential of gene therapy as a powerful tool in the field of Parkinson's Disease.

Methods

A systematic literature review was conducted to explore various gene therapy techniques, including RNAi, CRISPR-Cas9, ASOs, and AAV-mediated delivery. The literature search was performed using Google Scholar to identify relevant research papers, journal articles, studies, and clinical trials. The search was restricted to publications in peer-reviewed journals and included studies published from 2007 onward to ensure the inclusion of the most recent and relevant findings. To ensure source credibility, additional verification was conducted through databases such as PubMed and NCBI (Database arm of the US National Library of Medicine), cross-referencing findings to confirm the validity of challenges highlighted in the literature. Main goal was to identify research papers, journal articles, and studies that discuss the advantages and disadvantages of these techniques, along with fundamental explanations of each. For gene therapy clinical trials methodological framework, patient inclusion/exclusion criteria, study duration, sample size, and control groups used are documented.

Studies focusing on gene therapies or genetic editing techniques for PD, including preclinical research, clinical trials, and review articles on therapeutic strategies, were prioritized. Consideration was given to vector selection and delivery methods. These studies evaluated treatment effectiveness, potential side effects, and underlying mechanisms, reporting outcomes such as clinical efficacy, biomarker changes, adverse events, and safety profiles. Common inclusion criteria includes age restrictions, moderate to advanced disease severity, responsiveness to dopaminergic therapy, and the presence of motor complications.

Studies were excluded if they did not specifically address gene therapies for PD or were unrelated to the reviewed techniques (RNAi, CRISPR, ASOs, AAV). Additionally, studies lacking robust experimental design, statistical analysis, or appropriate controls were omitted or marked as limitations in the findings. Non-peer-reviewed publications or those presented in conference proceedings without proper validation were not included. Furthermore, studies without independent data verification were excluded from consideration. The studies with the

sample size, duration of follow-up were considered in evaluating the long-term efficacy and safety of gene therapies. Studies with smaller sample size or short-term follow-ups were noted as having limited predictive value for sustained therapeutic outcomes. Preference was given to studies that reported statistical significance and used appropriate control groups.

The findings are organized thematically, focusing on areas such as vector types (e.g., AAV, lentivirus), emerging technologies (e.g., ASOs, CRISPR), and clinical trial outcomes. Evaluation of the key factors like publication dates, peer-review status, author credentials, affiliations, and diversity in referenced sources to assess the reliability of the research. Additionally, gaps are identified in the literature, such as the lack of long-term data and challenges in delivering therapies across the blood-brain barrier.

This systematic approach ensured the literature review provided valuable and well-rounded insights into gene therapy approaches for Parkinson's disease.

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